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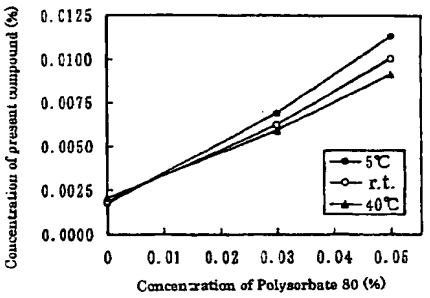
(54) EYE DROPS

(57) An object of the present invention is to formulate prostaglandin derivatives which are hardly soluble in water and liable to be adsorbed to a resinous container and prostaglandin derivatives which are liable to decompose when dissolved in water in ophthalmic solutions. Solubility of the prostaglandin derivatives in water is improved and the adsorption thereof to the resinous container can be remarkably inhibited by adding a nonionic surfactant such as polysorbate 80 or polyoxyethylene hydrogenated castor oil 60 to the ophthalmic solutions. The decomposition of the prostaglandin derivatives can be remarkably inhibited by adding an antioxidant such as disodium ethylenediaminetetraacetate or dibutylhydroxytoluene.

Fig. 1



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Description

Technical Field

[0001] The present invention relates to ophthalmic solutions comprising prostaglandin derivatives which are liable to be adsorbed to a container made of resin and hardly soluble in water as active ingredients, characterized in that concentrations of the prostaglandin derivatives in the ophthalmic solutions are prevented from lowering by adding a nonionic surfactant and/or an antioxidant.

Background Art

[0002] Natural prostaglandins are well-known as substances having various physiological activities. Using these prostaglandins as leading compounds, many prostaglandin derivatives have been researched. For example, as prostaglandin derivatives to be used for ophthalmic use, it is known that prostaglandin derivatives disclosed in Published Japanese Translation of PCT No. 501025/1991, and Japanese Laid-open Patent Publication Nos. 108/1990 and 71344/1999 are useful as therapeutic agents for glaucoma or ocular hypertension having intraocular pressure lowering effects.

[0003] As mentioned above, the prostaglandin derivatives are useful as the therapeutic agents for glaucoma or ocular hypertension, but some prostaglandin derivatives are hardly soluble in water and liable to be adsorbed to a resinous container. In order to formulate these prostaglandin derivatives in ophthalmic solutions, it is necessary to solve the problem of the solubility in water and a problem of a lowering in drug concentration due to the adsorption to the container. Since some prostaglandin derivatives are liable to decompose when dissolved in water, it is necessary to solve the problem of stability in order to formulate these prostaglandin derivatives in ophthalmic solutions. Since the adsorption of the drug to eye droppers and the decomposition of the drug in the ophthalmic solutions lead to a lowering in drug concentration in the ophthalmic solutions, it is an important subject for preparing ophthalmic solutions to solve these problems.

Disclosure of the Invention

[0004] Accordingly, the present inventors studied precisely a process for formulating prostaglandin derivatives which are liable to be adsorbed to a container made of resin and hardly soluble in water, into ophthalmic solutions. As a result, it was found that solubility of the prostaglandin derivatives in water is increased and adsorption thereof to the resinous container can be remarkably inhibited by adding a nonionic surfactant such as polysorbate 80 or polyoxyethylene hydrogenated castor oil 60 to the ophthalmic solutions. It was also found that decomposition of the prostaglandin derivatives can be remarkably inhibited by adding an antioxidant such as disodium ethylenediaminetetraacetate or dibutylhydroxytoluene.

[0005] The present invention relates to the ophthalmic solutions comprising the prostaglandin derivatives which are liable to be adsorbed to the container made of resin and hardly soluble in water (hereinafter referred to as "the prostaglandin derivatives") as active ingredients, characterized in that concentrations of the prostaglandin derivatives in the ophthalmic solutions are prevented from dropping by adding the nonionic surfactant and/or the antioxidant, and a method of preventing the concentrations from lowering.

[0006] The prostaglandin derivatives, so far as they are liable to be adsorbed to the resinous container and hardly soluble in water, are not limited in the present invention. Preferred examples of the prostaglandin derivatives are prostaglandin F2 α derivatives having fluorine atoms in their molecules disclosed in Japanese Laid-open Patent Publication Nos. 71344/1999 and 251225/1998. More preferred examples of the prostaglandin derivatives are difluoroprostaglandin F2 α derivatives disclosed in Japanese Laid-open Patent Publication No. 71344/1999. Particularly preferred examples of the prostaglandin derivatives are difluoroprostaglandin F2 α derivatives having two fluorine atoms at the 15th-position disclosed in Japanese Laid-open Patent Publication No. 71344/1999. Specific examples of the prostaglandin derivatives are 16-phenoxy-15-deoxy-15,15-difluoro-17,18,19,20-tetranorprostaglandin F2 α, 16-(3-chlorophenoxy)-15-deoxy-15,15-difluoro-17,18,19,20-tetranorprostaglandin F2 α, 16-phenoxy-15-deoxy-15,15-difluoro-13,14-dihydro-17,18,19,20-tetranorprostaglandin F2 α, alkyl esters thereof and salts thereof. Specific examples of the alkyl esters are lower alkyl esters such as methyl esters, ethyl esters, propyl esters, isopropyl esters, tert-butyl esters, pentyl esters and hexyl esters.

[0007] In the ophthalmic solution of the present invention, the prostaglandin derivatives are in a state where they are dissolved in water.

[0008] The expression "the prostaglandin derivatives are liable to be adsorbed to the resinous container" means that when the prostaglandin derivatives are stored in the resinous container in the form of an aqueous solution, a remaining rate (the remaining rate is a ratio of an amount of a prostaglandin derivative which keeps being effectively dissolved

in the ophthalmic solution to an amount of a prostaglandin derivative which was dissolved) drops remarkably. For example, when a concentration of a prostaglandin derivative in an aqueous solution is 0.001% (The "%" means % by weight as far as there is no proviso. The same definition is applied hereinafter.), the above-mentioned expression means a state where 40% or more (remaining rate in the solution: less than 60%), usually 40 to 60%, typically about 50% of the compound is adsorbed to a container made of polyethylene or polypropylene after the compound was stored in the container at 40°C for six months.

[0009] The prostaglandin derivatives which are hardly soluble in water are derivatives which require 1,000 ml or more of water in order to dissolve 1 g of the derivatives (the 13th revised Japanese Pharmacopoeia explanatory, general rule A-51 (1996)).

[0010] Nonionic surfactants are added in order to prevent the concentration of the prostaglandin derivatives from lowering by improving water-solubility of the prostaglandin derivatives in the ophthalmic solution and by inhibiting the adsorption to the resinous container. Specific examples of nonionic surfactants are polyoxyethylene fatty esters such as polysorbate 80 [poly(oxyethylene)sorbitan monooleate], polysorbate 60 [poly(oxyethylene)sorbitan monostearate], polysorbate 40 [poly(oxyethylene)sorbitan monopalmitate], poly(oxyethylene)sorbitan monolaurate, poly(oxyethylene) sorbitan trioleate and polysorbate 65 [poly(oxyethylene)sorbitan tristearate], polyoxyethylene hydrogenated castor oils such as polyoxyethylene hydrogenated castor oil 10, polyoxyethylene hydrogenated castor oil 40, polyoxyethylene hydrogenated castor oil 50 and polyoxyethylene hydrogenated castor oil 60, polyoxyethylene polyoxypropylene glycols such as polyoxyethylene (160) polyoxypropylene (30) glycol [Pluronic F68], polyoxyethylene (42) polyoxypropylene (67) glycol [Pluronic P123], polyoxyethylene (54) polyoxypropylene (39) glycol [Pluronic P85], polyoxyethylene (196) polyoxypropylene (67) glycol [Pluronic F127] and polyoxyethylene (20) polyoxypropylene (20) glycol [Pluronic L-44], polyoxyl 40 stearate and sucrose fatty esters. Preferred examples thereof are polysorbate 80 [poly(oxyethylene)sorbitan monooleate], polyoxyethylene hydrogenated castor oil 60 and polyoxyl 40 stearate. These nonionic surfactants can be used solely or in combination.

[0011] Preferred examples of the nonionic surfactants are polysorbate 80 [poly(oxyethylene)sorbitan monooleate] and polyoxyethylene hydrogenated castor oil 60, which are widely used as additives of ophthalmic solutions.

[0012] Antioxidants are added in order to prevent the concentration of the prostaglandin derivatives from lowering by inhibiting decomposition of the prostaglandin derivatives in the ophthalmic solution. Specific examples of antioxidants are sodium nitrite, ascorbic acid, L-ascorbic acid stearate, sodium hydrogensulfite, alphathioglycerin, ethylenediaminetetraacetic acid, erythorbic acid, cysteine hydrochloride, citric acid, tocopherol acetate, potassium dichloroisocyanurate, dibutylhydroxytoluene, 2,6-di-t-butyl-4-methylphenol, soybean lecithin, sodium thioglycollate, sodium thiomalate, natural vitamin E, tocopherol, ascorbyl pasthyminate, sodium pyrosulfite, butylhydroxyanisole, 1,3-butylene glycol, pentaerythtyl tetrakis[3-(3,5-di-t-butyl-4-hydroxyphenyl)]propionate, propyl gallate, 2-mercaptobenzimidazole and oxyquinoline sulfate. These antioxidants can be used solely or in combination.

[0013] Preferred examples of antioxidants are ethylenediaminetetraacetic acid, salts thereof and dibutylhydroxytoluene, which are widely used as additives of ophthalmic solutions. It is particularly preferable to combine ethylenediaminetetraacetic acid or the salt thereof with dibutylhydroxytoluene.

[0014] Examples of materials of the resinous container are polyethylene, polypropylene, polyethylene terephthalate, polyvinyl chloride, acrylic resins, polystyrene, polymethyl methacrylate and nylon 6. Preferred examples of the materials are polyethylene, polypropylene and polyethylene terephthalate. These resins can be high-density resins or low-density resins.

[0015] An amount (concentration) of the prostaglandin derivatives in the ophthalmic solution can be appropriately selected depending on object diseases, symptoms and the like, and is preferably 0.00005 to 0.05%.

[0016] An amount (concentration) of nonionic surfactants in the ophthalmic solution can be appropriately increased or decreased depending on the amount of the prostaglandin derivatives. It is preferable to select the concentration of nonionic surfactants which is five or more times that of the prostaglandin derivatives from the viewpoint of an increase in water-solubility of the prostaglandin derivatives. Further, it is preferable to select the concentration of nonionic surfactants which is ten or more times that of the prostaglandin derivatives from the viewpoint of a more certain assurance of water-solubility. The higher the concentration of the nonionic surfactants, the higher is the water-solubility of the prostaglandin derivatives. Accordingly, an upper limit of the concentration has no theoretical limitation, but is naturally required from the viewpoint of use for the ophthalmic solution. Namely, when nonionic surfactants are added at a high concentration, they exert adverse effects on ocular tissues such as cornea. Accordingly, the concentration of nonionic surfactants in the ophthalmic solution is usually 0.5% or less regardless of the concentration of the active ingredient.

[0017] An amount (concentration) of antioxidants in the ophthalmic solution can be appropriately selected depending on the kind of antioxidants. For example, when the antioxidant is disodium ethylenediaminetetraacetate, the concentration is usually 0.005 to 0.5%, preferably 0.01 to 0.1%. When the antioxidant is dibutylhydroxytoluene, the concentration is usually 0.00001 to 0.001%, preferably 0.00005 to 0.0005%.

[0018] Effects of the present invention are described in detail in later Examples. The water-solubility of the prostaglandin derivatives was improved and the adsorption thereof to the resinous container was remarkably inhibited by

adding the nonionic surfactant such as polysorbate 80 or polyoxyethylene hydrogenated castor oil 60 to the ophthalmic solutions. The decomposition of the prostaglandin derivatives in the ophthalmic solutions was effectively inhibited by adding the antioxidant such as disodium ethylenediaminetetraacetate or dibutylhydroxytoluene. These experimental results show that the concentration of the prostaglandin derivatives in the ophthalmic solution can be remarkably prevented from lowering.

[0019] When the ophthalmic solution of the present invention is prepared, pharmaceutically acceptable various additives such as an isotonic agent such as sodium chloride, potassium chloride, calcium chloride, glycerin or propylene glycol, a buffering agent such as boric acid, borax, citric acid, disodium hydrogen phosphate or ε-aminocaproic acid, and a preservative such as benzalkonium chloride, chlorhexidine gluconate, benzethonium chloride, sorbic acid, potassium sorbate, ethyl p-hydroxybenzoate or butyl p-hydroxybenzoate can be added in addition to the above-mentioned nonionic surfactants and antioxidants.

[0020] pH of the ophthalmic solution of the prostaglandin derivatives is preferably 3 to 8, particularly 4 to 7.

[0021] The ophthalmic solution of the present invention can be prepared by a widely-used process without special technique and operation.

[0022] It is hereinafter shown by Examples that the ophthalmic solutions of the present invention effectively prevent the concentration of the prostaglandin derivatives from lowering. These Examples do not limit the scope of the present invention, but are intended to make the present invention more clearly understandable.

Brief Description of Drawing

[0023] Fig. 1 is a graph showing effects of polysorbate 80 concentrations on solubility of the 16-phenoxy-15-deoxy-15,15-difluoro-17,18,19,20-tetranorprostaglandin F2 α isopropyl ester.

Best Mode for Carrying out the Invention

[0024] 16-Phenoxy-15-deoxy-15,15-difluoro-17,18,19,20-tetranorprostaglandin F2 α isopropyl ester (hereinafter referred to as "the present compound") was hereinafter used as a typical example of the prostaglandin derivatives in Examples.

1. Stability test 1

[0025] An effect of addition of a nonionic surfactant on preventing the present compound from adsorbing to a resinous container was studied. Remaining rates of the present compound were measured in a solution to which polysorbate 80 was added as the nonionic surfactant (formulation 1), a solution to which polyoxyethylene hydrogenated castor oil 60 (hereinafter referred to as "HCO60") was added as the nonionic surfactant (formulation 2) and a solution to which the nonionic surfactant was not added as control 1. Table 1 shows the concentrations of the components. The "%" in the table is % by weight.

Table 1

Components	Control 1	Formulation 1	Formulation 2
Present compound	0.001%	0.001%	0.001%
Polysorbate 80		0.01%	
HCO60			0.01%

Test method: Each solution was filleld into a container made of polyethylene and a container made of polypropylene and stored at 40 °C for six months. Then each remaining rate of the present compound in the solution was measured by a high-performance liquid chromatography method (hereinafter referred to as "the HPLC method").

Results and consideration: Table 2 shows results measured by the HPLC method.

Table 2

	Control 1	Formulation 1	Formulation 2
Remaining rates of the present compound in polyethylene container	42%	72%	63%
Remaining rates of the present compound in polypropylene container	56%	83%	80%

[0026] From Table 2, it is found that the remaining rate of the present compound in the solution of the formulation 1

or the formulation 2 to which the nonionic surfactant was added is higher than that of the control 1 to which the nonionic surfactant was not added in both resinous containers of polyethylene and polypropylene, and adsorption of the present compound to the resinous containers was remarkably inhibited.

2. Stability test 2

[0027] An inhibitory effect of addition of an antioxidant on decomposition of the present compound was studied. Remaining rates of the present compound were measured in a solution to which disodium ethylenediaminetetraacetate (hereinafter referred to as "the EDTA salt") was added as the antioxidant (formulation 3) and a solution to which the antioxidant was not added as control 2. Polysorbate 80 was added in an amount of 0.05% in each formulation as a solubilizing agent of the present compound. In order to evaluate only decomposition of the present compound, a glass container, which hardly exhibits adsorptivity of the present compound, was used as a storage container. Further, iron (III) chloride, which has concentrations described in terms of iron ion concentrations in Table 3, was added as a substance which promotes the decomposition of the present compound. The "%" in the table is % by weight.

Table 3

Components	Control 2	Formulation 3
Present compound	0.005%	0.005%
EDTA salt	-	0.05%
Iron ion	0.01 ppm	0.01 ppm

Test method: Each solution was filled into the glass container and stored at 40°C for six months. Then the remaining rate of the present compound in the solution was measured by the HPLC method. Results and consideration: Table 4 shows results measured by the HPLC method.

Table 4

	Control 2	Formulation 3
Remaining rate of the present compound	22%	79%

[0028] From Table 4, it is found that the remaining rate of the present compound in the solution of the formulation 3 to which the EDTA salt was added is higher than that of the control 2 to which the EDTA salt was not added, and the decomposition of the present compound was remarkably inhibited.

3. Stability test 3

[0029] An inhibitory effect of combined use of two antioxidants on decomposition of the present compound was studied. Remaining rates of the present compound were measured in a solution to which the two antioxidants, i.e., the EDTA salt and dibutylhydroxytoluene were added as the antioxidants (formulation 4) and a solution to which the antioxidants were not added as control 3. Polysorbate 80 was added in an amount of 0.05% in each formulation as a solubilizing agent of the present compound. In order to evaluate only decomposition of the present compound, a glass container, which hardly exhibits adsorptivity of the present compound, was used as a storage container. Further, a storage temperature was raised to 60°C in order to promote the decomposition of the present compound. The "%" in the table is % by weight.

Table 5

Components	Control 3	Formulation 4
Present compound	0.005%	0.005%
EDTA salt	-	0.05%
Dibutylhydroxytoluene	-	0.0001%

Test method: Each solution was filled into the glass container and stored at 60°C for two weeks. Then the remaining rate of the present compound in the solution was measured by the HPLC method. Results and consideration: Table 6 shows results measured by the HPLC method.

Table 6

	Control 3	Formulation 4
Remaining rate of the present compound	19.3%	99%

[0030] From Table 6, it is found that the remaining rate of the present compound in the solution of the formulation 4 to which the EDTA salt and dibutylhydroxytoluene were added as the antioxidants is higher than that of the control 3 to which the antioxidants were not added, and the decomposition of the present compound was remarkably inhibited.

4. Stability test 4

[0031] Effects of addition of the nonionic surfactant and the antioxidant on preventing the present compound from adsorbing to the resinous container and on inhibiting decomposition of the present compound were studied. A remaining rate of the present compound was measured in an ophthalmic solution to which polysorbate 80 and the EDTA salt were added as the nonionic surfactant and the antioxidant respectively (formulation 5). The "%" in the table is % by weight.

Table 7

Components	Formulation 5
Present compound	0.005%
Polysorbate 80	0.05%
EDTA salt	0.05%

Test method: The ophthalmic solution of formulation 5 was filled into a container made of polypropylene and stored at 40°C for six months, and then the remaining rate of the present compound in the ophthalmic solution was measured by the HPLC method.

Result and consideration: Table 8 shows a result measured by the HPLC method.

Table 8

	Formulation 5
Remaining rate of the present compound	95.6%

[0032] From Table 8, it is found that the remaining rate of the present compound is high even after the ophthalmic solution of formulation 5 was stored in the container made of polypropylene for a long period, and a concentration of the present compound in the ophthalmic solution was remarkably prevented from lowering.

5. Solubility test

[0033] In order to formulate a drug which is hardly soluble in water in an ophthalmic solution, it is necessary to devise to dissolve the drug in water. Since the nonionic surfactant acts as the solubilizing agent, the following solubility tests were performed in order to make sure of its required amount.

Test method: The present compound having a concentration exceeding solubility and polysorbate 80 were added to 10 ml of water, the mixtures were stirred at 5°C, room temperature and 40°C for 24 hours respectively and then centrifuged at 20,000 rpm, and concentrations of the present compound contained in the supernatants were measured by the HPLC method.

Results and consideration: Fig. 1 shows results measured by the HPLC method. The "%" in the figure is % by weight.

[0034] From Fig. 1, it is found that solubility of the present compound increases depending on amounts of polysorbate 80, and the amounts of polysorbate 80 (nonionic surfactant) are preferably five or more times the concentration of the present compound, considering storage conditions and a change in concentration of the present compound. Water-solubility of the present compound at low temperatures is higher than that at high temperatures.

[0035] Effects of the present invention are as follows. The solubility of the prostaglandin derivatives in water is improved and the adsorption thereof to the resinous container is remarkably inhibited by adding nonionic surfactants such as polysorbate 80 and polyoxyethylene hydrogenated castor oil 60 to the ophthalmic solutions. The decomposition of the prostaglandin derivatives in the ophthalmic solutions is effectively inhibited by adding antioxidants such as dis-

odium ethylenediaminetetraacetate and dibutylhydroxytoluene. These experimental results show that the concentrations of the prostaglandin derivatives in the ophthalmic solution were remarkably prevented from lowering.

Industrial Applicability

[0036] The present invention provides ophthalmic solutions comprising prostaglandin derivatives which are liable to be adsorbed to a resinous container and hardly soluble in water as active ingredients, characterized in that concentrations of the prostaglandin derivatives in the ophthalmic solutions are prevented from lowering by adding a nonionic surfactant and/or an antioxidant.

Claims

1. An ophthalmic solution comprising a prostaglandin derivative which is liable to be adsorbed to a container made of resin and hardly soluble in water as an active ingredient, **characterized in that** a concentration of the prostaglandin derivative in the ophthalmic solution is prevented from lowering by adding a nonionic surfactant and/or an antioxidant.

2. The ophthalmic solution as claimed in claim 1, **characterized in that** adsorption of the prostaglandin derivative to the resinous container is inhibited by adding the nonionic surfactant.

3. The ophthalmic solution as claimed in claim 1, **characterized in that** decomposition of the prostaglandin derivative is inhibited by adding the antioxidant.

4. The ophthalmic solution as claimed in claim 1 or 2, wherein the nonionic surfactant is polysorbate 80 or polyoxyethylene hydrogenated castor oil 60.

5. The ophthalmic solution as claimed in claim 1 or 3, wherein the antioxidant is ethylenediaminetetraacetic acid, a salt thereof or dibutylhydroxytoluene.

6. The ophthalmic solution as claimed in any one of claims 1 to 5, wherein a material of the resinous container is polyethylene, polypropylene, polyethylene terephthalate or polyethylene naphthalate.

7. The ophthalmic solution as claimed in any one of claims 1 to 6, wherein a concentration of the nonionic surfactant is at least five times that of the prostaglandin derivative.

8. The ophthalmic solution as claimed in any one of claims 1 to 7, wherein the prostaglandin derivative is a prostaglandin F2 α derivative or a salt thereof having fluorine atoms in its molecule.

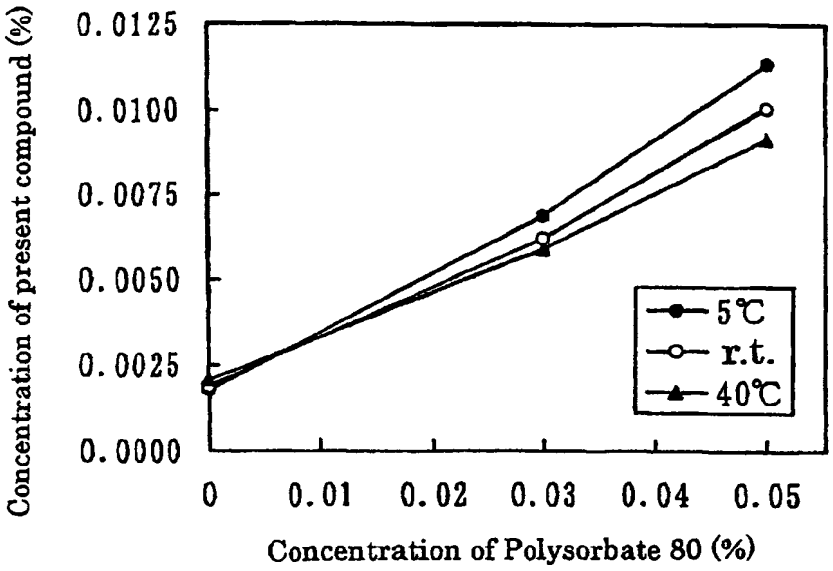
9. The ophthalmic solution as claimed in claim 8, wherein the prostaglandin derivative is a difluoroprostaglandin F2 α derivative or a salt thereof.

10. A method of preventing a concentration loweing of a prostaglandin derivative which is liable to be adsorbed to a resinous container and hardly soluble in water, the prostaglandin derivative being contained in an ophthalmic solution as an active ingredient, **characterized by** adding a nonionic surfactant and/or an antioxidant to the ophthalmic solution.

11. A method of inhibiting adsorption of a prostaglandin derivative which is liable to be adsorbed to a resinous container and hardly soluble in water, to the container which contains an ophthalmic solution comprising the prostaglandin derivative as an active ingredient, **characterized by** adding a nonionic surfactant to the ophthalmic solution.

12. A method of inhibiting decomposition of a prostaglandin derivative which is liable to be adsorbed to a resinous container and hardly soluble in water, the prostaglandin derivative being contained in an ophthalmic solution as an active ingredient, **characterized by** adding an antioxidant to the ophthalmic solution.

Fig. 1


Concentration of present compound (%)
0.0125
0.0100
0.0075
0.0050
0.0025
0.0000
0
0.01
0.02
0.03
0.04
0.05
Concentration of Polysorbate 80 (%)
5℃
r.t.
40℃

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP01/07928

A. CLASSIFICATION OF SUBJECT MATTER
Int.Cl[7] A61K31/5575, A61K9/08, A61K47/34, A61K47/44, A61K47/18, A61K47/10, A61P27/02

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
Int.Cl[7] A61K31/5575, A61K9/08, A61K47/34, A61K47/44, A61K47/18, A61K47/10, A61P27/02

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
Jitsuyo Shinan Koho 1922-1996 Toroku Jitsuyo Shinan Koho 1994-2001
Kokai Jitsuyo Shinan Koho 1971-2001 Jitsuyo Shinan Toroku Koho 1996-2001

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CA (STN), MEDLINE (STN)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 603800 A (Alcon Laboratories, Inc.), 29 June, 1994 (29.06.94), Full text & AU 665287 B & CA 2112027 A & JP 6-316525 A & US 5565492 A	1-12
X	EP 850926 A (Santen Pharmaceutical Co., Ltd.), 01 July, 1998 (01.07.98), Full text & CA 2225761 A & US 5886035 A	1,2,4,7-11
Y	& US 5985920 A & JP 11-071344 A	3,5,6,12
X	EP 930296 A (Santen Pharmaceutical Co., Ltd.), 21 July, 1999 (21.07.99), Full text & JP 10-251225 A	1,2,4,7-11
Y		3,5,6,12

☒ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
31 October, 2001 (31.10.01)	13 November, 2001 (13.11.01)
Name and mailing address of the ISA/ Japanese Patent Office	Authorized officer
Facsimile No.	Telephone No.

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP01/07928

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5486540 A (Allergan, Inc.), 23 January, 1996 (23.01.96), Full text & WO 95/11682 A & AU 9480844 A & US 5486540 A & EP 725643 A & JP 9-506081 A	3,5,6,12